REPORT DOCUMENTATION PAGE

AD-A257 156

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 1992	3. Reprint

4. TITLE AND SUBTITLE

(see title on reprint)

5. FUNDING NUMBERS

PE: NWED QAXM

WU: 00178

6. AUTHOR(S)

Male et al.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Armed Forces Radiobiology Research Institute
8901 Wisconsin Ave.
Bethesda, MD 20889-5603

8. PERFORMING ORGANIZATION REPORT NUMBER

SR92-31

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Defense Nuclear Agency
6801 Telegraph Road
Alexandria, VA 22310-3398

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

DTIC
ELECTE
OCT. 2 8 1992
S B D

14. SUBJECT TERMS		15. NUMBER OF PAGES 8
		16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED		

Cisplatin-induced conditioned taste aversion: attenuation by dexamethasone but not zacopride or GR38032F

Paul C. Mele, John R. McDonough, David B. McLean and Kevin P. O'Halloran

Behavioral Sciences Department, Armed Forces Radiobiology Research Institute, Bethesda, MD 20889-5145, USA

The 5-HT$_3$ receptor antagonists zacopride and GR38032F are highly effective inhibitors of emesis induced by ionizing radiation and chemotherapeutic drugs such as cisplatin. The present study evaluated zacopride and GR38032F for efficacy in inhibiting the formation of the conditioned taste aversion (CTA) induced by cisplatin or lithium chloride in rats. The glucocorticoid dexamethasone, which has been reported to be effective against both the emetic and CTA-inducing effects of cisplatin, was included as a reference compound. When administered alone by i.p. injection, zacopride (0.1-10 mg/kg), GR38032F (10 mg/kg) and cisplatin (0.32-1.8 mg/kg) induced a CTA to an 0.1% saccharin solution; lower doses of each compound were ineffective. When administered as a pretreatment, neither zacopride (0.001-0.1 mg/kg) nor GR38032F (0.01-10 mg/kg) attenuated the CTA induced by cisplatin (0.32 and 0.56 mg/kg) or lithium chloride (10 mg/kg). In contrast, dexamethasone (0.32 and 1.0 mg/kg) attenuated the CTA induced by 0.32 but not 0.56 mg/kg of cisplatin. In an attempt to evaluate higher doses of zacopride against cisplatin without the potentially confounding factor that these doses by themselves induce a CTA, rats were injected with zacopride on three separate days prior to the aversion conditioning session. This pre-exposure treatment blocked the formation of the zacopride-induced CTA, but did not improve the efficacy of zacopride in attenuating the cisplatin-induced CTA. These results suggest that neither the cisplatin- nor the lithium-induced CTA in rats are due to effects that are sensitive to 5-HT$_3$ receptor blockade.

5-HT$_3$ receptor antagonists; Zacopride; GR38032F; Dexamethasone; Cisplatin; Taste aversion (conditioned)

1. Introduction

Antagonists of the serotonin type-3 (5-HT$_3$) receptor (Richardson and Buchheit, 1980) show great promise in controlling nausea and vomiting induced by treatment with cytotoxic anticancer agents. 5-HT$_3$ antagonists attenuate chemotherapeutic drug- and ionizing radiation-induced emesis in animals and nausea and emesis in humans (King and Makale, 1991; Sanger,

1990). 5-HT$_3$ antagonists are effective against highly emetogenic drugs such as cisplatin, and, at therapeutically effective dosages, lack the serious adverse side effects that frequently occur with the most commonly used antiemetics (Laszlo, 1983).

Rodents, while devoid of the emetic reflex, have nevertheless been used in the evaluation of behavioral effects of antiemetic drugs. One approach with rodents has been to determine if antiemetic drugs block the formation of the conditioned taste aversion (CTA) produced by cytotoxic agents that induce emesis in species that are capable of vomiting (Cairnie and Leach, 1982; Levy et al., 1974; Landauer et al., 1985; Rabin and Hunt, 1983; Revusky and Martin, 1988). The CTA paradigm involves pairing the ingestion of a normally preferred substance (e.g., a saccharin solution) with the administration of a drug or toxicant. A CTA is indicated when animals avoid ingestion of the substance when it is subsequently presented.

Although CTAs have often been attributed in the past to effects related to sickness, nausea or emesis, it has since become apparent that such effects cannot provide a general account of CTA learning (Gamzu et

al., 1985; Hunt and Amit, 1987). However, it has been argued that emetic-related mechanisms may be involved in the formation of CTAs induced by certain types of agents (Garcia et al., 1985; Grant, 1987). This argument is based, in part, on results showing that CTA and emesis can share some underlying neural circuitry. Consistent with this argument are the findings that both CTA formation and emesis induced by cisplatin (McCarthy and Borrison, 1984; B. Rabin, personal communication) or ionizing radiation (Grant, 1987; Rabin and Hunt, 1986) are blocked or attenuated by lesions of the area postrema, the lower brainstem area known as the chemoreceptor trigger zone (Borrison, 1974). Moreover, the findings that rats, ferrets and humans have high levels of 5-HT$_3$ binding sites in the area postrema and adjacent structures (Barnes et al., 1988, 1990; Kilpatrick et al., 1988; Waeber et al., 1989), suggest that 5-HT$_3$ receptors located here could be involved in CTA learning and/or emesis. Corroborative data in ferrets suggest that these receptors may be one site where 5-HT$_3$ antagonists act to inhibit cisplatin-induced emesis (Higgins et al., 1989).

The present study evaluated the 5-HT$_3$ antagonists zacopride (Smith et al., 1988b) and GR38032F (Butler et al., 1988) for efficacy in attenuating the formation of a CTA induced by cisplatin in rats. The glucocorticoid dexamethasone was used as a reference compound for evaluating attenuation of the cisplatin-induced CTA (cf. Revusky and Martin, 1988). Additionally, zacopride and GR38032F were tested against the toxicant lithium chloride which is used frequently to induce a CTA and is capable of inducing emesis (Baldessarini, 1980; Rabin and Hunt, 1990).

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats, obtained from Charles River breeders, were housed individually in plastic Microisolator cages containing sterilized hardwoodchip bedding. Commercial rodent chow was freely available throughout the study. Purified tap water was freely available until the start of training. Animal holding rooms were maintained at 21 ± 1°C with 50 ± 10% relative humidity. A 12-h light/dark cycle was in effect with lights on from 06:00 to 18:00.

2.2. Conditioning procedure

All training and testing were conducted in the homecage. During the initial 10-day training period, a single water bottle was presented for 30 min/day. On day 11, the conditioning day, a novel saccharin solution (0.1% sodium saccharin, w/v) was substituted for wa-

ter; rats that failed to drink the saccharin solution were dropped from the experiment. All vehicle and drug injections were given on day 11 after removal of the saccharin solution (see below). Separate groups of rats were used for each vehicle and drug condition. A single water bottle was available again for 30 min on day 12. On day 13 the choice-test was conducted. The choice-test consisted of presenting two bottles simultaneously for 30 min; one contained water and the other contained the saccharin solution. The relative saccharin intake on day 13 (ml of saccharin solution intake divided by ml of total fluid intake) was used as the index of the CTA.

2.3. Drug treatments

The CTA-inducing effects of zacopride, GR38032F and cisplatin were determined initially. Subsequently, zacopride, GR38032F and dexamethasone were evaluated for efficacy in attenuating the CTA induced by cisplatin or lithium chloride. Zacopride, GR38032F and dexamethasone were administered immediately after the drinking session, while cisplatin and lithium chloride were administered 30 min after drinking. Sterile physiological saline was the vehicle for zacopride and lithium, while sterile water was the vehicle for GR38032F, cisplatin and dexamethasone. When evaluating drug interactions, each rat received two injections (drug or vehicle) at the appropriate times after drinking. All injections were given i.p. in a volume of 1 ml/kg. Zacopride and GR38032F were kindly supplied by A.H. Robbins, Inc., Richmond, VA and Glaxo Group Research Limited, Middlesex, England, respectively. Dexamethasone, cisplatin and lithium chloride were purchased from Sigma Chemicals, St. Louis, MO.

2.4. Data analysis

Relative saccharin solution intake during the choice-test was analyzed by one- and two-way analyses of variance and subsequent Dunnett's or Newman-Keuls' post-hoc tests. A significance level of $P \leq 0.05$ was used.

3. Results

Figure 1 shows that a significant CTA was produced by zacopride at 0.1–10 mg/kg (top panel, $F_{(6,63)}$ = 6.84, $P < 0.001$); lower doses were ineffective. A subsequent independent replication of a portion of the zacopride dose-effect function (not shown) confirmed that 0.1 mg/kg but not 0.01 and 0.03 mg/kg produced a significant CTA, $F_{(3,31)}$ = 3.23, $P < 0.05$. GR38032F produced a significant CTA at 10 mg/kg only (middle panel, $F_{(6,58)}$ = 6.87, $P < 0.001$). Cisplatin produced a

significant CTA at 0.32–1.8 mg/kg while at 3.2 mg/kg relative saccharin solution intake was reduced although this failed to achieve statistical significance (bottom panel, $F(5,53) = 5.05$, $P = 0.001$).

The lack of a significant decrease in relative saccharin solution intake at 3.2 mg/kg of cisplatin was most likely due to the nonspecific disruption in fluid intake that occurred after treatment with this dose. On the day prior to aversion conditioning, water intakes (means ± S.E.M.) were 21.6 ± 1.0 and 21.4 ± 0.6 ml in the vehicle and cisplatin treatment groups, respectively. During the choice-test, total fluid intakes for these two groups were 19.4 ± 0.8 and 10.3 ± 2.4 ml. In addition, the higher doses of cisplatin proved toxic in that six of ten rats given 3.2 mg/kg, and three of ten rats given 1.8 mg/kg, died within one week following cisplatin administration.

Figure 2 shows that the CTA produced by 0.32 or 0.56 mg/kg of cisplatin (middle and bottom panels, respectively) was not altered significantly by pretreatment with zacopride. After each zacopride plus cisplatin treatment, saccharin intake was significantly lower than after vehicle administration, but was not significantly different than after treatment with vehicle plus cisplatin ($F = (4,37) = 9.26$, $P < 0.001$ for 0.32 mg/kg cisplatin, and $F = (4,42) = 4.67$, $P < 0.005$ for 0.56 mg/kg cisplatin). A lower dose of cisplatin (0.18

Fig. 2. Effect of zacopride pretreatment on the cisplatin-induced conditioned taste aversion. Each panel shows the effect of zacopride given prior to one dose of cisplatin: 0.18 mg/kg (top), 0.32 mg/kg (middle) and 0.56 mg/kg (bottom). Each point indicates the mean intake of 8–10 rats except for the group given 0.1 mg/kg of zacopride + 0.32 mg/kg of cisplatin where $n = 6$; error bars indicate one S.E.M. * $P < 0.05$ versus vehicle (V), * $P < 0.05$ versus cisplatin (CP), Newman–Keuls test.
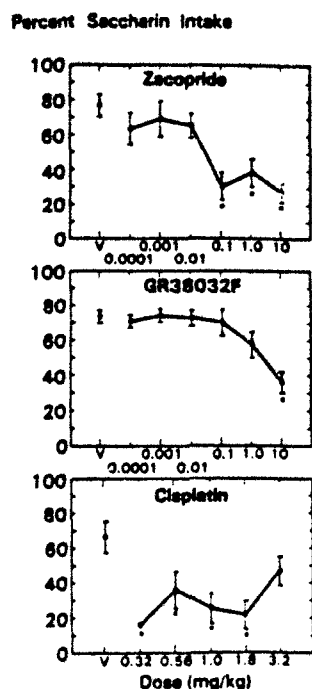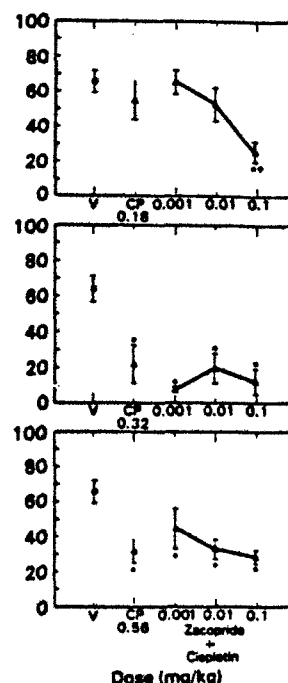

Fig. 1. Dose–effect curves for conditioned taste aversions induced by zacopride (top), GR38032F (middle) and cisplatin (bottom). Each point indicates the mean intake of 8–11 rats; error bars indicate one S.E.M. * $P < 0.05$ versus vehicle (V), Dunnett's test.

mg/kg) failed to produce a significant CTA (top panel). When 0.1 mg/kg of zacopride was administered as the pretreatment to 0.18 mg/kg of cisplatin, saccharin solution intake was reduced significantly compared to both vehicle and cisplatin, $F(4,42) = 3.76$, $P = 0.01$; this reduction is consistent with the effect of 0.1 mg/kg of zacopride administered alone (fig. 1).

Similar to what was observed with zacopride as a pretreatment, GR38032F was ineffective in altering the CTA produced by cisplatin (fig. 3). Saccharin intake following each GR38032F plus cisplatin treatment was significantly less than following vehicle treatment and was not significantly different than following vehicle plus cisplatin ($F(4,39) = 5.03$, $P < 0.005$ for 0.32 mg/kg cisplatin and $F(4,44) = 5.49$, $P = 0.001$ for 0.56 mg/kg cisplatin).

It was considered possible that the CTA-inducing effect of the higher doses of zacopride and GR38032F prevented or masked an attenuation of the cisplatin-induced CTA. Therefore, an attempt was made to eliminate this potentially confounding factor by administering zacopride on several occasions prior to condition-

Percent Saccharin Intake

Percent Saccharin Intake

Zacopride (mg/kg)

Fig. 4. Effect of pre-exposure to zacopride on the zacopride-induced conditioned taste aversion. Each point indicates the mean intake of 8-9 rats; error bars indicate one S.E.M. * P < 0.05 versus vehicle (V). Dunnett's test.
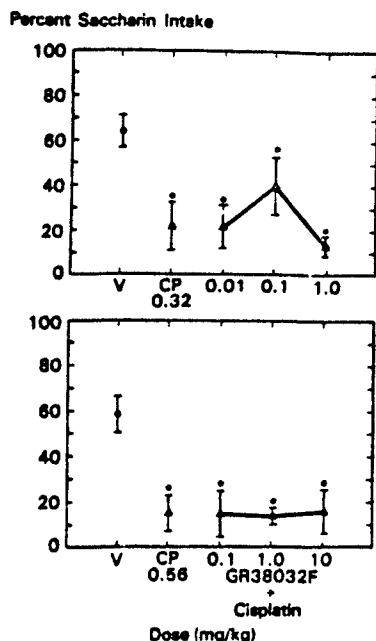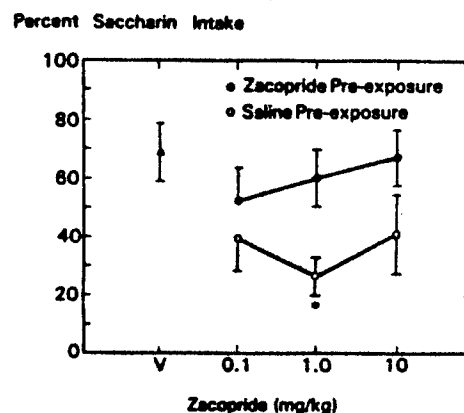
Fig. 3. Effect of GR38032F pretreatment on the cisplatin-induced conditioned taste aversion. Each panel shows the effect of GR38032F given prior to one dose of cisplatin (CP): 0.32 mg/kg (top) and 0.56 ng/kg (bottom). Each point indicates the mean intake of 8-10 rats; error bars indicate one S.E.M. * P < 0.05 versus vehicle (V), Newman-Keuls' test.

Figure 5 presents the effects of zacopride pre-exposure on the efficacy of zacopride in blocking the cisplatin-induced CTA; the pre-exposure procedure was the same as that described above. Cisplatin produced a significant reduction in saccharin solution intake at 0.32 (top) and 0.56 (bottom) mg/kg; these reductions were not attenuated by zacopride (1.0 or 10 mg/kg)

ing. This pre-exposure treatment has been shown to reduce the CTA-inducing efficacy of a variety of agents (e.g., Switzman et al., 1981).

The pre-exposure procedure consisted of giving each of six treatment groups a single injection after water drinking on training days 3, 5 and 8. Pairs of groups were injected with either vehicle (saline) or one of three doses (0.1, 1.0 or 10 mg/kg) of zacopride. For each pair of groups, the dose of zacopride used for pre-exposure was also the dose used subsequently to establish the CTA. A seventh group of rats was injected with saline three times during the pre-exposure period, and then received saline on the conditioning day.

Figure 4 shows that pre-exposure to zacopride prevented formation of the zacopride-induced CTA. On the test day, saccharin intakes of groups pre-exposed to zacopride were consistently greater than intakes of groups pre-exposed to saline. Two-way ANOVA on the data of these six groups revealed a main effect of pre-exposure condition, F(1,43) = 8.04, P < 0.01, while the main effect of zacopride dose and the zacopride dose by pre-exposure condition interaction were not significant. Moreover, relative to the group treated only with vehicle, the zacopride-induced aversion was most pronounced in the groups pre-exposed to saline.
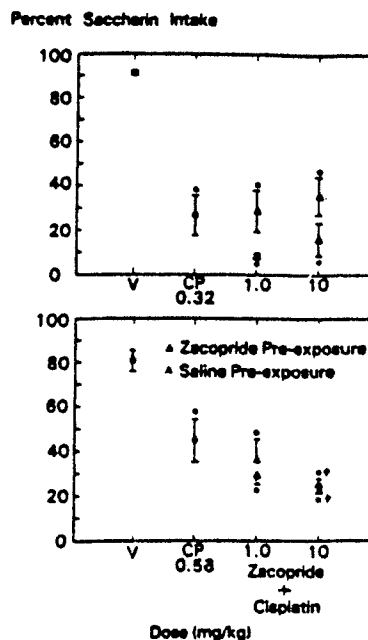
Percent Saccharin Intake

Dose (mg/kg)

Fig. 5. Effect of pre-exposure to zacopride on the efficacy of zacopride in blocking the cisplatin-induced conditioned taste aversion. Each point indicates the mean intake of 10-12 rats in the top panel and 5-9 rats in the bottom panel; error bars indicate one S.E.M. * P < 0.05 versus vehicle (V), * P < 0.05 versus cisplatin (CP), Newman-Keuls' test.

regardless of whether animals were pre-exposed to saline or zacopride.

Pre-exposure to zacopride was ineffective in another regard. In this case, there was a slight but significant enhanc :ment of the CTA when the highest doses of zacopride and cisplatin were administered together, and this enhancement was not attenuated by pre-exposure to zacopride. This can be seen in the lower panel of figure 5 where 10 mg/kg of zacopride plus 0.56 mg/kg of cisplatin produced a greater reduction in saccharin solution intake than saline plus 0.56 mg/kg of cisplatin regardless of the pre-exposure treatment.

The effects of zacopride and GR38032F pretreatment on the lithium chloride-induced CTA are presented in fig. 6. In the zacopride function, $F(4,46) = 4.43$, $P < 0.005$, the lithium-induced aversion was not altered significantly by zacopride. Similarly, in the GR38032F function, $F(4,50) = 2.89$, $P < 0.05$, the effect of lithium did not appear to be altered. In this function however, lithium did not reduce intake significantly.

The effects of dexamethasone pretreatment on the cisplatin-induced CTA are shown in fig. 7. When administered prior to vehicle, neither 0.32 nor 1.0 mg/kg of dexamethasone altered saccharin solution intake significantly, although a small reduction was evident at the higher dose. Both doses of dexamethasone attenuated the reduction in saccharin solution intake produced by 0.32 mg/kg of cisplatin, with the higher dose being more effective, $F(5,54) = 4.73$, $P < 0.001$. After dexamethasone pretreatment, 0.32 mg/kg of cisplatin no longer reduced saccharin intake significantly compared to vehicle treatment. In contrast, neither dose of dexamethasone attenuated significantly the CTA induced by 0.56 mg/kg of cisplatin, $F(5,50) = 10.55$, $P < 0.001$.
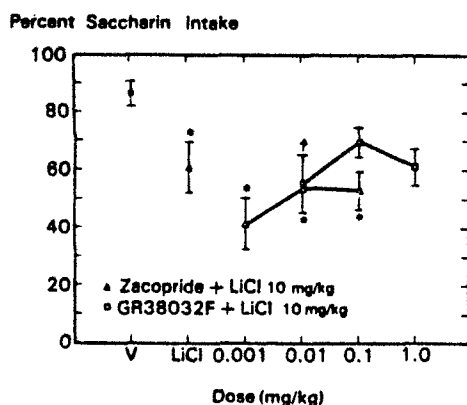
Percent Saccharin Intake

Fig. 6. Effect of pretreatment with zacopride or GR38032F on the lithium chloride-induced conditioned taste aversion. Each point indicates the mean intake of 9-11 rats; error bars indicate one S.E.M. * * P < 0.05 (Newman-Keuls' test) versus vehicle (V) for the zacopride plus lithium and GR38032F plus lithium functions, respectively.
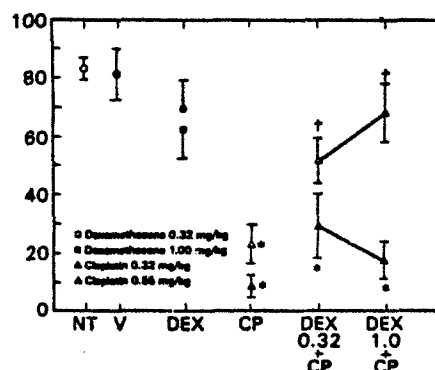
Percent Saccharin Intake

Fig. 7. Effect of dexamethasone pretreatment on the cisplatin-induced conditioned taste aversion. Each point indicates the mean intake of 8-10 rats; error bars indicate one S.E.M. * P < 0.05 versus vehicle (V), * P < 0.05 versus cisplatin (CP), Newman-Keuls' test. The group given no treatment (NT) was excluded from the statistical analysis.

To control for possible effects of the injection procedure, an additional group of rats which received no injections at any time was tested. Comparison between the no-treatment and vehicle conditions in figure 7 shows that the injection procedure itself did not alter saccharin intake.

4. Discussion

5-HT$_3$ antagonists are potent and effective inhibitors of chemotherapeutic drug- and ionizing radiation-induced emesis in cats, dogs, ferrets and monkeys and nausea and emesis in humans (King and Makale, 1991; Sanger, 1990). Those reports strongly suggest that 5-HT$_3$ receptor mechanisms are critically involved in the expression of nausea and emesis induced by cytotoxic treatments. The present study sought to extend the evaluation of 5-HT$_3$ antagonists by determining if either zacopride or GR38032F could block the formation of a cisplatin-induced CTA in rats. However, under the conditions in effect here, neither zacopride nor GR38032F showed significant efficacy in this regard. Therefore, in contrast to the findings on emesis, the present results indicate that the cisplatin-induced CTA is not susceptible to treatment with these 5-HT$_3$ antagonists, and presumably to the blockade of 5-HT$_3$ receptors.

High levels of 5-HT$_3$ binding sites have been found in the area postrema and adjacent structures of rats, ferrets and humans (Barnes et al., 1988, 1990; Kilpatrick et al., 1988; Waeber et al., 1989). These lower brain stem structures have been shown to be involved in cisplatin-induced emesis in cats (McCarthy and Bor-

rison, 1984) and CTA formation in rats (B. Rabin, personal communication), since lesions of the area postrema block both responses. Recent findings suggest that 5-HT$_3$ binding sites in the area postrema of the ferret are functional receptors involved in the regulation of cisplatin-induced emesis (Higgins et al., 1989). The present investigation suggests that 5-HT$_3$ binding sites in the area postrema of rats are unlikely to be involved in the regulation of the cisplatin-induced CTA. The function of 5-HT$_3$ binding sites in the area postrema of the rat has yet to be determined.

It seems unlikely that the failure of zacopride and GR38032F to attenuate the cisplatin-induced CTA can be attributed solely to certain procedural factors. Doses of the antagonists used here inhibit or reduce emesis induced by high doses (3–10 mg/kg) of cisplatin in ferrets and cats (Higgins et al., 1989; Smith et al., 1988a), and can induce behavioral changes in rats (Costall et al., 1988; Jones et al., 1988). Several of those studies showed that zacopride and GR38032F are effective when injected i.p. as was done here. The rapid onset and long duration of action of these compounds (Butler et al., 1988; Costall et al., 1988; Higgins et al., 1989; Jones et al., 1988; Smith et al., 1989) suggest that the timing of the injections used here was appropriate.

Zacopride and GR38032F induced an aversion at the higher doses tested. This does not necessarily preclude the possibility that these doses could have reduced the cisplatin-induced aversion (e.g., Peele et al., 1988). The pre-exposure manipulation was an attempt to directly reduce the aversion-inducing effect of zacopride. Although pre-exposure to zacopride prevented the subsequent formation of the zacopride-induced aversion, it did not improve the efficacy of zacopride in reducing the cisplatin-induced aversion. Thus, the failure of zacopride to attenuate the aversion produced by cisplatin does not appear to be due to CTA-inducing properties of zacopride itself.

Zacopride induced a CTA at doses of 0.1–10 mg/kg. In ferrets, similar and lower doses (0.003–3.0 mg/kg) that are antiemetic have been shown to induce behavioral (locomotor stimulation and depression) and gastrointestinal (emesis and defecation) disturbances (King, 1990). The mechanisms of these side effects appear to be complex and include action at several types of serotonergic receptors (5-HT$_3$ and 5-HT$_4$) as well as cholinergic and dopaminergic involvement (Bhandari and Andrews, 1991; King, 1990). Conceivably, some or all of these mechanisms could underly the zacopride-induced CTA although this is currently unknown. In contrast to zacopride, GR38032F induced a CTA only at the very high dose of 10 mg/kg which is well above doses sufficient for the control of emesis. Although 10 mg/kg does not appear to have been tested in ferrets, data on 1–5 mg/kg are available

(Endo et al, 1991; Higgins et al., 1989); there was no mention of GR38032F-induced behavioral or gastrointestinal disturbances in either of those reports. The presently available data suggest that zacopride and GR38032F differ in terms of the type of side effects produced and in potency for inducing a CTA.

The glucocorticoid dexamethasone was shown to attenuate the cisplatin-induced CTA. Thus, the procedure used here was sufficiently sensitive to detect drug-induced reduction of the cisplatin-induced aversion. This finding confirms and extends a previous study that reported attenuation of the cisplatin-induced CTA by dexamethasone when a somewhat different procedure (i.e., one involving multiple conditioning and test trials and one-bottle tests) was used (Revusky and Martin, 1988). Clinically, dexamethasone can inhibit nausea and emesis induced by cisplatin and other chemotherapeutics (Al-Idrissi et al., 1988; Cassileth et al., 1983; Parry and Martin, 1991). Thus, despite the negative findings obtained with zacopride and GR38032F, the present study provides further evidence that the CTA paradigm can be useful in the evaluation of certain types of agents used for the treatment of nausea and emesis.

Dexamethasone reduced the aversion produced by the lower (0.32 mg/kg) but not the higher (0.56 mg/kg) dose of cisplatin. Similarly, dexamethasone attenuated the CTA induced by lower but not higher doses of ionizing radiation (Cairnie and Leach, 1982) and lithium chloride (Revusky and Martin, 1988). Thus, as was stated in those earlier reports, the CTA paradigm appears to be most useful for evaluating certain drug interactions when low doses of the aversion-inducing agent are used (see also Landauer et al., 1985). However, in addition to the results obtained with cisplatin, preliminary data presented here indicate that neither zacopride nor GR38032F attenuated the CTA induced by a low dose of lithium chloride. In contrast, the formation of the lithium-induced CTA in rats is blocked by lesioning the area postrema (Ritter et al., 1980). Taken together, these findings suggest that 5-HT$_3$ binding sites in the area postrema of the rat (Kilpatrick et al., 1988) are unlikely to directly mediate the formation of the lithium-induced CTA.

The mechanism underlying the cisplatin-induced CTA is unknown. In contrast, the antiemetic efficacy of 5-HT$_3$ antagonists, as well as a variety of other data, indicate a prominent role of 5-HT in cytotoxic drug- and radiation-induced emesis (Andrews et al., 1988). Although the present data do not support the involvement of 5-HT$_3$ receptors in the cisplatin-induced CTA, they cannot rule out other means by which 5-HT could be involved. Alternatively, it has been suggested that cytotoxic agents may stimulate synthesis and release of other substances (e.g., arachidonic acid, prostaglandins, substance P, free radicals) (Andrews et al., 1988), and

perhaps one or more of these agents are involved. Inhibition of prostaglandin synthesis may be of particular interest because this has been suggested as being one means by which dexamethasone attenuates both CTA formation and emesis (Cairnie and Leach, 1982). However, because glucocorticoids are involved in a wide range of physiological functions and exert a variety of pharmacological effects (Haynes and Murad, 1980), the mechanism involved here can only be determined by further systematic evaluation.

Acknowledgements

References

Al-Idrissi, H.Y., E.M. Ibrahim, K.A. Abdullah, W.A. Ababtain, H.A. Boukhary and H.M.K. Macaulay, 1988, Antiemetic efficacy of high-dose dexamethasone, Br. J. Cancer 57, 308.

Andrews, P.L.R., W.G. Rapeport and G.J. Sanger, 1988, Neuropharmacology of emesis induced by anti-cancer therapy, Trends Pharmacol. Sci. 9, 334.

Baldessarini, R.J., 1980, Drugs and the treatment of psychiatric disorders, in: Goodman and Gilman's the Pharmacological Basis of Therapeutics, 6th Ed., eds. A.G. Gilman, L.S. Goodman and A. Gilman (Macmillan, New York) p. 391.

Barnes, N.M., B. Costall, R.J. Naylor and F.D. Tattersall, 1988, Identification of 5-HT$_3$ recognition sites in the ferret area postrema, J. Pharm. Pharmacol. 40, 586.

Barnes, J.M., N.M. Barnes, B. Costall, J.F.W. Deakin, J.W. Ironside, G.J. Kilpatrick, R.J. Naylor, J.A. Rudd, M.D.C. Simpsin, P. Slater and M.B. Tyers, 1990, Identification and distribution of 5-HT$_3$ recognition sites within the human brainstem, Neurosci. Lett. 111, 80.

Bhandari, P. and P.R. Andrews, 1991, Preliminary evidence for the involvement of the putative 5-HT$_4$ receptor in zacopride- and copper sulfate-induced vomiting in the ferret, Eur. J. Pharmacol. 204, 273.

Borison, H.L., 1974, Area postrema: Chemoreceptive trigger zone for vomiting-is that all?, Life Sci. 14, 1807.

Butler, A., J.M. Hill, S.J. Ireland, C.C. Jordan and M.B. Tyers, 1988, Pharmacological properties of GR38032F, a novel antagonist at 5-HT$_3$ receptors, Br. J. Pharmacol. 94, 397.

Cairnie, A.B. and K.E. Leach, 1982, Dexamethasone: a potent blocker for radiation-induced taste aversion in rats, Pharmacol. Biochem. Behav. 17, 305.

Cassileth, A.B., E.J. Luck, S. Torri, N. DiNubile and S.L. Gerson, 1983, Antiemetic efficacy of dexamethasone therapy in patients receiving chemotherapy, Arch. Int. Med. 143, 1347.

Costall, B., A.M. Domeney, P.A. Gerrard, M.E. Kelly and R.J. Naylor, 1988, Zacopride: anxiolytic profile in rodent and primate models of anxiety, J. Pharm. Pharmacol. 40, 302.

Endo, T., M. Minami, Y. Monma, M. Yoshioka, R. Saito, Y. Toshimitsu and S.R. Parvez, 1991, Effect of odansetron, a 5-HT$_3$ antagonist, on copper sulfate-induced emesis in the ferret, Biogenic Amines 8, 79.

Gamzu, E., G. Vincent and E. Boff, 1985, A pharmacological perspective of drugs used in establishing conditioned food aversions, Ann. N.Y. Acad. Sci. 443, 231.

Garcia, J., P.S. Lassiter, F. Bermudez-Rattoni and D.A. Deems, 1985, A general theory of aversion learning, Ann. N.Y. Acad. Sci. 443, 8.

Grant, V.L., 1987, Do conditioned taste aversions result from activation of emetic mechanisms?, Psychopharmacology 93, 405.

Haynes, R.C. and F. Murad, 1980, Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of adrenocortical steroid biosynthesis, in: Goodman and Gilman's the Pharmacological Basis of Therapeutics, 6th Ed., eds. A.G. Gilman, L.S. Goodman and A. Gilman (Macmillan, New York) p. 1466.

Higgins, G.A., G.J. Kilpatrick, K.T. Bunce, B.J. Jones and M.B. Tyers, 1989, 5-HT$_3$ receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret, Br. J. Pharmacol. 97, 247.

Hunt, T. and Z. Amit, 1987, Conditioned taste aversion induced by self-administered drugs: paradox revisited, Neurosci. Biobehav. Rev, 11, 107.

Jones, B.J., B. Costall, A.M. Domeney, M.E. Kelly, R.J. Naylor, N.R. Oakley and M.B. Tyers, 1988, The potential anxiolytic activity of GR38032F, a 5-HT$_3$-receptor antagonist, Br. J. Pharmacol. 93, 985.

Kilpatrick, G.J., B.J. Jones and M.B. Tyers, 1988, The distribution of specific binding of the 5-HT$_3$ receptor ligand [^{3}H] GR65630 in rat brain using quantitative autoradiography, Neurosci. Lett. 94, 156.

King, G.L., 1990, Emesis and defecations induced by the 5-hydroxytryptamine (5-HT$_3$) receptor antagonist zacopride in the ferret, J. Pharmacol. Exp. Ther. 253, 1034.

King, G.L. and M.T. Makale, 1991, Postirradiation emesis, in: Nausea and Vomiting: Recent Research and Clinical Advances, eds. J. Kucharczyk, D.J. Stewart and A.D. Miller (CRC Press, Boca Raton) p. 103.

Landauer, M.R., R.L. Balster and L.S. Harris, 1985, Attenuation of cyclophosphamide-induced taste aversions in mice by prochlorperazine, delta-9-tetrahydrocannabinol, nabilone and levonantradol, Pharmacol. Biochem. Behav. 23, 259.

Laszlo, J., 1983, ed., Antiemetics and Cancer Chemotherapy (Williams and Wilkins, Baltimore).

Levy, C.J., M.E. Carroll, J.C. Smith and K.G. Hofer, 1974, Antihistamines block radiation-induced taste aversions, Science 186, 1044.

McCarthy, L.E. and H.L. Borison, 1984, Cisplatin-induced vomiting eliminated by ablation of the area postrema in cats, Cancer Treatm. Rep. 68, 401.

Parry, H. and K. Martin, 1991, Single-dose i.v. dexamethasone – an effective anti-emetic in cancer chemotherapy, Cancer Chemother. Pharmacol. 28, 231.

Peele, D.B., J.D. Farmer and R.C. MacPhail, 1988, Behavioral consequences of chelator administration in acute cadmium toxicity, Fund. Appl. Toxicol. 11, 416.

Rabin, B.M. and W.A. Hunt, 1983, Effects of antiemetics on the acquisition and recall of radiation- and lithium chloride-induced conditioned taste aversions, Pharmacol. Biochem. Behav. 18, 829.

Rabin, B.M. and W.A. Hunt, 1986, Mechanisms of radiation-induced conditioned taste aversion learning, Neurosci. Biobehav. Rev. 10, 55.

Rabin, B.M. and W.A. Hunt, 1990, Taste aversion learning in the ferret: limits on conditioned and unconditioned stimuli, Soc. Neurosci. Absts. 16, 1245.

Revusky, S. and G.R. Martin, 1988, Glucocorticoids attenuate taste aversions produced by toxins in rats, Psychopharmacology 96, 400.

Richardson, B.P. and K.H. Buchheit, 1988, The pharmacology, distribution and function of 5-HT$_3$ receptors, in: Neuronal Serotonin, eds. N.N. Osborne and M. Hamon (John Wiley and Sons, New York) p. 485.

236

Ritter, S., J.J. McGlone and K.W. Kelly, 1980. Absence of lithium-induced taste aversion after area postrema lesion. Brain Res. 201, 501.

Sanger, G.J., 1990, New antiemetic drugs, Can. J. Physiol. Pharmacol. 68, 314.

Smith, W.L., R.S. Alphin, C.B. Jackson and L.F. Sancilio, 1989, The antiemetic profile of zacopride, J. Pharm. Pharmacol. 41, 101.

Smith, W.L., E.M. Callahan and R.S. Alphin, 1988a, The emetic activity of centrally administered cisplatin in cats and its antagonism by zacopride, J. Pharm. Pharmacol. 40, 142.

Smith, W.W., L.F. Sancilio, J.B. Owera-Atepo, R.J. Naylor and L. Lambert, 1988b, Zacopride, a potent 5-HT₃ antagonist, J. Pharm. Pharmacol. 40, 301.

Switzman, L., B. Fishman and Z. Amit, 1981, Pre-exposure effects of morphine, diazepam and delta-9-THC on the formation of conditioned taste aversions, Psychopharmacology (Berlin) 74, 149.

Waeber, C., D. Hoyer and J.M. Palacios, 1989, 5-Hydroxytryptamine₁ receptors in the human brain: autoradiographic visualization using [³H]ICS 205-30, Neuroscience 31, 393.